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| 10/552,023      | 07/27/2006  | Robin Alec Fairhurst | PR/4-33154A         | 6898             |

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| EXAMINER |
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SEAMAN, D MARGARET M

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1625

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07/24/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                                       |                                         |  |
|------------------------------|---------------------------------------|-----------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/552,023  | <b>Applicant(s)</b><br>FAIRHURST ET AL. |  |
|                              | <b>Examiner</b><br>D. Margaret Seaman | <b>Art Unit</b><br>1625                 |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 June 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/9/07 &amp; 10/3/05</u> .                                    | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

This application was filed 7/27/2006 and is a 371 of PCE/EP04/03516 (4/2/2004).

Claims 1-20 have been canceled per paper dated 6/8/2009. Claims 21-32 are before the Examiner.

### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 29 is rejected under 35 U.S.C. 112, 1<sup>st</sup> paragraph, because the specification, while possibly being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the compounds such as presently claimed. In addition, it is presumed that “prevention” of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit the symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. “The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the

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predictability or unpredictability of the art, h) and the breadth of the claims”, In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) As discussed above, preventing diseases required identifying those patients who will acquire the disease before the disease occurs. This would require extensive and potentially open-ended clinical research on healthy subjects. B) The passage spanning lines of the instant specification, lists the diseases applicant intends to prevent. C) There are no working examples of such preventive procedure in a man or animal in the specification. D) The claims rejected are drawn to the medical prevention and are therefore physiological in nature. E) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted with disease before the fact. F) The artisan using Applicant’s invention would be a board certified physician who specializes in treating diseases. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, In re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of the practitioners in that art, Genetech vs. Novo Nordisk, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent diseases generally. That is, the skill is so low that no compound effective generally against diseases has ever been found let alone one that can prevent such conditions. G) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved”, and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427

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F.2d 833, 839, 166 USPQ 18, 214 (CCPA 1970). H) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by formula (I).

The Examiner suggests deletion of the word “prevention”.

1. Claims 21, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while maybe enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. “The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of guidance or direction presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case, the important factors leading to a conclusion of undue experimentation are c) the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. There are no working examples of any solvate formed. The claims are drawn to solvates, yet the numerous examples presented all fail to produce a single solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the

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required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is ... no evidence that such compounds even exist.” The same circumstances appear to be true here. There is no evidence that solvates of the instantly claimed compounds actually exist; if they did, they would have been formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. G) The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., “Solid State Chemistry and its Application, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and not part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West says, “it is not usually possible to predict whether solid solution will form, or if they do form, what is their compositional extent”. Thus, in the absence of experimentation, one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two or a half of a molecule of solvent added per molecule of host. In the same paragraph on page 365, West explains that it is possible to make meta--stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. H) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term “solvate. Thus, the scope is broad.

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2. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the nexus between the modulation of the  $\beta$ 2-adrenoreceptor and a useful treatment of a disease/condition. Modulation of a receptor involves antagonism, inhibition, agonism and others. These modulations are sometimes opposite reactions to the same receptor. It is not seen where the instant specification adequately describes the nexus between the modulation of the  $\beta$ 2-adrenoreceptor and a useful treatment of a single disease or condition.

3. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to

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make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**The nature of the invention:** The nature of the invention is the method of treating a disorder that is modulated by the  $\beta$ 2-adrenoreceptor .

**The state of the prior art:** The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The predictability in the art:** It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of  $\beta$ 2-adrenoreceptor would make a difference in the disease. Hence, in the absence of a showing of a



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nexus between any and all known diseases and the modulation of  $\beta$ 2-adrenoreceptor, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of  $\beta$ 2-adrenoreceptor. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor

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representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

**The presence or absence of working examples:** There are no working examples of the instantly claimed compounds inhibiting or modulating anything or treating airway diseases.

**The amount of direction or guidance present:** The guidance present in the specification is that of the compounds inhibit  $\beta$ 2-adrenoreceptor and therefore can treat any disease that this is involved. The specification does not seem to enable a correlation between the mediation of  $\beta$ 2-adrenoreceptor and the treatment of any and all diseases.

**The breadth of the claims:** The claims are drawn to the treatment of any and all diseases mediated by the  $\beta$ 2-adrenoreceptor with the compound of claim 21.

**The quantity of experimentation needed:** The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of  $\beta$ 2-adrenoreceptor and then would further need to determine which of the claimed compounds would provide treatment of the disease.

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**The level of the skill in the art:** The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

#### ***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

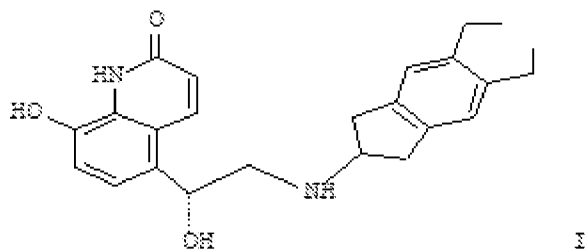
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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 21-32 are rejected under 35 U.S.C. 102(b,e) as being anticipated by WO 2002045703, WO 2000075114 and Cuenoud (US Patent 6800643 (10/2004, effective filing date of 12/2000) and US Patent 7008951 (3/2006, effective filing date of 12/2000) and US Patent 6878721 (3/2005, filing date 6/1999)). Cuenoud teaches compounds such as



for the treatment of airway

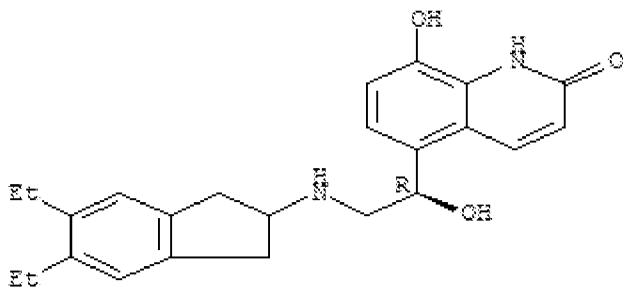
disorders for WO 2002, US Patent '643 and '951. This anticipates the instant claims. Cuenoud teaches compounds such as

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RN 312753-06-3 CA

CN 2(1H)-Quinolinone, 5-[(1R)-2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



as B2-

adrenoceptor agonists.

6. Claims 21-32 are rejected under 35 U.S.C. 102(e) as being anticipated by 7250426, 7417051, 7317102 and 7534890.

'890 teaches compounds such as col 7 line 35 that anticipates the instant claims. '102 teaches compounds such as compound of col 23 line 15 where R4 is cyclopentyl. '051 teaches compounds such as col 4 line 50 that anticipate the instant claims. '426 teaches compounds such as col 3 line 60 that anticipate the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D. Margaret Seaman  
Primary Examiner  
Art Unit 1625

/D. Margaret Seaman/  
Primary Examiner, Art Unit 1625